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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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EXAMINER	
KAUFMAN, C	
ART UNIT	**PAPER NUMBER**
1646	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/346,069	Applicant(s) KEYT ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-33* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 18-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *15-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 12 is acknowledged.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 19-21, 23, 25, 27, 29-32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Since the claimed nucleic acid is naturally occurring (see rejection under 35 USC 102 below) and is not claimed as purified and/or isolated, the claims do not show the hand of man involved in the invention and, therefore, are unpatentable. See MPEP § 706.03(a) and 2105. It is noted that "contains" is open language, so claims such as 29 are not limited to modification of only Phe 17 and Glu 64 of said native.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 18 is rejected under the judicially created doctrine of double patenting over claim 1 of U. S. Patent No. 6,057,428 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Since claim 18 is drawn to a composition of matter but recites only what is set forth in claim 1 of the patent, then the same thing is being claimed.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim 15 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,057,428. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to the artisan of ordinary skill in the art to add a pharmaceutically acceptable carrier to the polypeptide of claim 18 of the instant application in order to produce antibodies to VEGF or the described variant by methods well known and routine in the art.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 21 and dependent claims 15 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 is indefinite because a composition must comprise more than one component. It is unclear what the composition includes besides the purified polypeptide, and it is unclear if the polypeptide is an active ingredient of the composition or merely present in trace amounts. Knowing whether the polypeptide is critical to the composition is necessary to understand the breadth of the claim. If the polypeptide is the active ingredient, this rejection could be obviated by adding to the end of the claim a phrase such as, "and a carrier".

Claim 21 is indefinite because it is unclear how "at least one" (claim 19) is different from

"one or more" (claim 21) of said amino acids is modified. It is unclear how dependent claim 21 is meant to differ from the claim upon which it depends.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There does not appear to be support in the instant specification for modification of the following amino acids as recited in the newly added claims: Phe 17, Ile 46 and Ile 43. The extensive list of mutations in the tables of the specification does not include mutation of these amino acids. As a result, it does not appear that applicants were in possession of the claimed nucleic acids.

Claims 18 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a VEGF variant which is the same as native VEGF except that it contains at least one amino acid modification in the KDR and/or FLT-1 region, wherein KDR is the binding domain of the KDR receptor and FLT-1 is the binding domain for the FLT-1 receptor, such that said amino acid modification results in modification of the binding affinity of said region(s) with respect to the binding affinity of the KDR and/or FLT-1 receptors to native VEGF, does not reasonably provide enablement for VEGF variants which differ in amino acid sequence from native VEGF in areas outside the KDR or FLT-1 region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims encompass a VEGF variant which has one or more modifications in the KDR

or FLT-1 region. However, the variant by definition in the specification may have modifications outside those regions, the modification may be other than an amino acid change (e.g., substitution), and it is not clear how modification(s) outside the binding region(s) affect binding affinity. These variants are not enabled by the specification.

The claims encompass a protein that has little if any structural resemblance to VEGF. The reason is that the encoded protein is a VEGF *variant* that contains modifications--not necessarily amino acid substitutions (p. 17)--in the KDR and/or FLT-1 region. Other examples of amino acid mutations are deletions of from 1 to about 30 amino acids, internal insertions of up to 10 amino acids, terminal attachments of unrestricted length, amino acid substitutions, or amino acid modifications (e.g., p. 21, lines 8-9, and p. 19, lines 6-9). Therefore, as with the flanking regions, the structure of the binding domains does not need to resemble the structure of the native protein. Because of the lack of sufficient structural limitations in the claims and the broad functional limitation, this is an extremely broad claim and resembles a single means claim. The specification has taught specific amino acid(s) which, when substituted for the corresponding amino acid(s) in the native VEGF, significantly alter binding characteristics to the KDR or FLT-1 receptor compared to the wildtype VEGF (*e.g.*, TABLES 4-6), but has not taught which amino acids outside the binding regions can be altered without affecting binding characteristics. Nor has the specification disclosed whether insertions or deletions within the binding regions (as opposed to substitutions) can alter binding. Not only would the biological property of the protein with mutations in both the binding and flanking regions be unpredictable, but the variant protein structure resulting from mutations/modifications would also be.

In addition to mutations within the KDR and/or FLT-1 domains, a variant may have mutations "in all other parts of the molecule so as to impart interesting properties that do not affect the overall properties of the variants with respect to the domains from 78 to 95 and 60 to 70" (p. 16, lines 25-28). Further, the functional limitation of the claims requires that the variant have a different binding affinity to the KDR and/or FLT-1 receptor compared to native VEGF. This means that not only can the variant have a significantly increased binding affinity compared to the native form, but also that the variant does not have to bind at all.

For these reasons, which include broad claim language, the complex nature of the invention in terms of both structure and binding, the limited teachings and examples in the

specification and the paucity of VEGF structural binding information in the prior art, it would require undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Tischer et al. (US Patent 5,219,739, reference 11 cited by Applicants).

Tischer et al. teach both the human and bovine VEGF protein (Figures 7 and 6, respectively). Amino acids 63, 64, 67, 82, 84, 86, and 79, 83 of bovine VEGF differ from the native human VEGF of Figure 7. These residues fall within the range of residues at positions about 60-70 that make up the FLT-1 region and position about 78-95 that make up the KDR region. While Tischer et al. are silent as to differential binding affinities of the bovine compared to native human VEGF, one would reasonably expect, absence evidence to the contrary, that binding affinities would be different--even if only minutely different--because it is generally accepted by those of ordinary skill in the ligand/receptor art that species homologues of a ligand which have different sequences will have different affinities for the same receptor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tischer et al. (US Patent 5,219,739).

Tischer et al. is relied upon for the teachings as applied to claim 18 above. Tischer et al.

also teach conditioned medium containing secreted human VEGF protein (Examples 9 and 13), which constitutes a composition comprising a VEGF and a pharmaceutically acceptable carrier. The different binding properties of the forms of VEGF and their therapeutic advantages are also discussed (col. 2, lines 22-61). Tischer et al. do not teach such a composition comprising bovine VEGF.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce secreted bovine VEGF as taught by Tischer et al. for human VEGF in order to compare binding properties of the different VEGF proteins and evaluate their therapeutic potential as suggested by Tischer et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Claire M. K

Patent Examiner, Art Unit 1646

May 2, 2001